II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 39-47 and 63-89 were pending and rejected in the Office Action mailed May 12, 2006. Applicants have amended claims 39 and 68 based on the support in the specification at least at page 9, lines 9-18; page 27, line 17. Claims 41-45 have been cancelled.

Claims 90 and 91 have been added. Support for these claims can be found in the specification at least at page 72, lines 4-10. Therefore, no new matter has been added.

Accordingly, claims 39-40, 46-47, and 63-91 are pending.

B. Claims 39, 41, 63, 64, 84, and 85 Are Not Anticipated

The Action rejects claims 39, 41, 63, 64, 84 and 85 under 35 U.S.C. §102(b) as anticipated by MacDonald *et al.*, *Science* 269:688-690, 1995 ("MacDonald"). MacDonald is said to teach an assay involving an antibody that specifically interacts with a human Fortilin polypeptide. Applicants respectfully traverse this rejection.

Claim 39 recites a method involving "assaying whether the candidate substance inhibits Fortilin polypeptide binding activity, wherein a candidate substance that inhibits binding activity is a modulator of the Fortilin polypeptide." This claim and claims dependent from it (41, 63, and 64) are not anticipated because this element is not taught by MacDonald. MacDonald does not teach assaying for inhibition of Fortilin polypeptide binding activity. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987).

Moreover, rejected claims 84 and 85 are dependent on independent claim 68, which recites a method involving "contacting a candidate modulator with a recombinant cell expressing a Fortilin polypeptide . . . . " Dependent claims have all of the limitations of the claims from

which they depend and because MacDonald does not teach this element of claim 68, claims 84 and 85 are not anticipated by MacDonald. The Action acknowledges this because claim 68 was not rejected as anticipated by MacDonald.

For the foregoing reasons, Applicants respectfully request this rejection be withdrawn.

C. Claims 39, 41, 63, 64, 84, and 85 Are Not Obvious

1. Claims Are Not Obvious over MacDonald and Gold

The Action rejects claims 39-42, 44, and 65 under 35 U.S.C. § 103(a) as being obvious over MacDonald , and further in view of Gold *et al.* (U.S. Patent 5,270,163) ("Gold"). The Action contends that a method for identifying a nucleic acid modulator that specifically binds to and modulates the function of a polypeptide was known it the art. It cites to Gold and alleges it would have been routine to one of ordinary skill in the art to identify a substance that specifically binds to and modulates the function of a protein. The Action also argues one of ordinary skill in the art would have been motivated to identify modulators of the histamine releasing function possessed by the protein taught by MacDonald because MacDonald teaches that histamine is involved in mediating the inflammatory response and can be useful in studying human allergic diseases. It also says there would have been a reasonable expectation of success. Applicants respectfully traverse this rejection.

As discussed above, claim 39 recites a method involving "assaying whether the candidate substance inhibits Fortilin polypeptide binding activity, wherein a candidate substance that inhibits binding activity is a modulator of the Fortilin polypeptide." The MacDonald reference does not teach this. Moreover, neither does Gold because it does not talk about assaying for a candidate substance that inhibits *Fortilin* polypeptide binding activity. The Action does not identify anywhere in Gold where a Fortilin polypeptide is disclosed. Therefore, the issue becomes why would one of skill in the art combine MacDonald and Gold, as is required for a

valid *prima facie* case of obviousness. MPEP §2142. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP § 2143.01 citing *In re Mills,* 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

The contention in the Action is that there is a motivation to find a modulator for Fortilin because of its function identified in the Gold paper. However, this contention is not only illusory, but also this is not the requisite motivation to *combine references.* Nowhere in the Gold paper does it discuss looking for inhibitors of Fortilin (or HRF, as it is termed in MacDonald), particularly those inhibitors that inhibit Fortlin's binding activity. Furthermore, simply because a protein may be interesting to study does not mean there is a motivation to combine MacDonald with any screening method disclosure, much less particularly the Gold reference. If this were the case, the Gold reference could be used to render obvious *any* screening method claim because of its broad disclosure. This simply cannot be the case.

Furthermore, there is no reasonable expectation of success in achieving the claimed invention. Because neither MacDonald nor Gold provide any functional information related to Fortilin binding activity, the skilled artisan would not know 1) that Fortilin binding activity could be inhibited and 2) how to evaluate whether Fortilin polypeptide binding activity had been inhibited. This is in contrast to the disclosure of the present invention in which Fortilin polypeptide binding activity is discussed and demonstrated. Therefore, the combination of MacDonald and Gold also fails to provide a reasonable expectation of success.

Accordingly, a proper *prima facie* case of obviousness has not been made and Applicants respectfully request this rejection be withdrawn.

2. Claims Are Not Obvious over MacDonald and Dehlinger

The Action rejects claims 39-42, 44, and 66 under 35 U.S.C. § 103(a) as being obvious over MacDonald , and further in view of Dehlinger *et al.* (WO 97/19749) ("Dehlinger"). The Action makes the same contentions as above except it argues that Dehlinger teaches screening of small molecules instead Gold teaching about screening with nucleic acids. Applicants respectfully traverse this rejection.

As discussed above, a proper *prima facie* case of obviousness has not been made. The combination of MacDonald and Dehlinger is as defective as MacDonald and Gold because Dehlinger, like Gold, does provide any basis for combining its teaching about screening methods specifically with the Fortilin polypeptide of Gold. Not only is there no suggestion or motivation to combine these references, but also, there is no reasonable expectation of success for the reasons described earlier. Dehlinger, or MacDonald or Gold for that matter, says anything about Fortlin polypeptide binding activity. The skilled artisan would have no expectation of success without knowing that Fortilin possessed such activity and without knowing how to test for such activity (for example, without knowledge of what it binds to, such as p53 or MCL1, as is disclosed in the instant specification). The Dehlinger/MacDonald combination fails to provide a *prima facie* case of obviousness.

Accordingly, Applicants respectfully request this rejection be withdrawn.

D. Claims Are Definite

The Action rejects claims 39-47, 63-67, 84 and 85 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as their invention. It contends that methods claims require an active or positive step that accomplishes the goals for the method which are stated in the methods' preamble. It says the rejected claims lack such a step because the additional method step(s) is not

sufficiently set forth. The Action alleges that the problem with the claims is that there is no requirement or active or positive step in the claims that the method actually results in identification of the modulator. It contends that the claims are indefinite because the scope f the claim is unclear as to whether the steps indicated in (a) and (b) of claim 39 are sufficient to identify the modulator. Applicants respectfully traverse this rejection.

Rejected claim 39 sets forth:

> A method of identifying a modulator of a Fortilin polypeptide comprising:
> (a) contacting a Fortilin polypeptide with at least 70% of its amino acids identical with a candidate substance; and
> (b) assaying whether the candidate substance inhibits Fortilin polypeptide binding activity, wherein a candidate substance that inhibits binding activity is a modulator of the Fortilin polypeptide.

The claim sets forth the positive steps to be done to achieve the claimed invention. In a screening method, there is no guarantee of a positive result, however, the concept of a screening method is that one could identify such modulators by employing the recited steps. Applicants do not understand what positive step is missing from the claim. Those are all the steps to be done in order to achieve the preamble.

As to the scope of the claims, they are set forth by the limitations of steps (a) and (b). There is no basis for saying that the scope is unclear because additional steps may be involved. The Action provides no suggestions as to what those steps might be, in all likelihood because there are no missing positive steps.

Applicants note that the Gold patent relied upon by the Action sets forth as claim 1:

> 1. A method for identifying nucleic acid ligands of a target compound from a candidate mixture comprised of single stranded nucleic acids each having a region of randomized sequence, said, method comprising:
> a) contacting the candidate mixture with the target, wherein nucleic acids having an increased affinity to the target relative to the candidate mixture may be partitioned from the remainder of the candidate mixture;

b) partitioning the increased affinity nucleic acids from the remainder of the candidate mixture; and

c) amplifying the increased affinity nucleic acids, in vitro, to yield a ligand-enriched mixture of nucleic acids, whereby nucleic acid ligands of the target compound may be identified.

This claim does not set forth any positive step other than the steps the skilled artisan employs to try and identify a ligand as set forth in the preamble—much like the presently rejected claims. The claim in Gold does state, "whereby nucleic acid ligands of the target compound may be identified" but this is not a positive step, nor does it indicate that such a ligand is positively identified.

In addition, the rejection of claims 84 and 85 appears erroneous as these do not depend from claim 39. Applicants contend this rejection has no basis and respectfully request its withdrawal.

E. Claims Are Adequately Described

The Action rejects claims 39-47 and 63-89 as failing to comply with the written description requirement. The Action argues that the specification has not adequately described a sufficient number of "representative species" encompassed by the claims because of the huge number of possible variants encompassed by the claims and the limited guidance provided in the specification with respect to identifying the biologically active variants encompassed by the claims. Applicants respectfully traverse this rejection.

Independent claims 39 and 64 are directed to methods involving a Fortilin polypeptide that has at least 90% of its amino acids identical to SEQ ID NO:2. SEQ ID NO:2 is 172 amino acids in length. Therefore, the genus of Fortilin polypeptides include any polypeptide with fewer than 17 amino acid changes relative to SEQ ID NO:2. Applicants contend that in providing SEQ ID NO:2, the skilled artisan would readily appreciate that Applicants had described an adequate

number of species that are covered by the claims. A computer program or a high school biology student could also discern the limited number of polypeptides covered by the claims.

Moreover, Applicants emphasize that in providing SEQ ID NO:2 and setting forth that the Fortilin polypeptide has at least 90% of its amino acids identical to SEQ ID NO:2, Applicants have fulfilled the written description requirement because these are structural limitations readily discernible to the skilled artisan as showing that Applicants were in possession of the invention. The written description requirement may be "satisfied through sufficient description of a representative number of species . . . by disclosure of relevant identifying characteristics, i.e., structure or other physical and/or chemical properties . . . sufficient to show that applicant was in possession of the claimed genus." MPEP § 2163, subsection 3(a)(ii), quoting from *Regents of the Univ. of California v. Eli Lilly,* 119 F.3d 1559, 1568, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997).

The reliance on *Fiddes v. Baird*, 30 USPQ2d 1481, and *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016 is inappropriate given that both of these cases involved claims with no structural limitations as set forth in the rejected claims. Those cases are not relevant here because Applicants limit the claims with respect to SEQ ID NO:2 and they disclose SEQ ID NO:2.

Moreover, Applicants note that they provided the decision on appeal in *Ex Parte Friedberg* not because it is binding precedent, but because it provides insight into what the Board of Patent Appeals and Interferences understand the requirements of written description to be. The claims in *Friedberg* recited structural limitations based on a SEQ ID NO, similar to the situation here. That was the basis for the Board's reversing the examiner's written description rejection on that case, and it did not have to do specifically with the fact that the claims were drawn to a pol κ polypeptide. This distinction between *Friedberg* and the current case is irrelevant. The relevant similarity between the two cases is that in providing a full polypeptide sequence and then having

claims reciting structural limitations of a polypeptide based on that sequence is sufficient to satisfy the written description requirement.

For the foregoing reasons, Applicants respectfully request the written description rejection be withdrawn.

F. Claims Are Enabled

The Action also rejects claims 39-47 and 63-89 as not enabled under 35 U.S.C. §112, first paragraph. Specifically, it contends that the specification is not enabling for 1) performing the methods using a non-isolated cell/polypeptide that is in a transgenic animal or for 2) the variant Fortilin polypeptides encompassed by the claims.

1. Cells in Transgenic Animals

The Action first contends that the claims cover a recombinant cell in which the cell is in a transgenic animal. The Action then argues that there was unpredictability in the state of the prior art at the time the invention in making a transgenic animal that expresses a Fortilin polypeptide.

Applicants take issue with the fact that the Action focuses on one particular embodiment—a recombinant cell that is in a transgenic animal—and argues that the claim is not enabled because of that one embodiment. The claims are directed to a screening method which may or may not involve a recombinant cell, which may or may not be in a transgenic animal. There are many more embodiments of the claim that fully enabled and not contested by the Action.

Moreover, the evidence relied upon does not show that the prior art in the area of transgenic animals was unpredictable or that the invention could not be done. The papers cited in the Action at best indicate that things such as integration sites and species can affect the extent of transgene expression. However, these are phenomena that do not prevent the use of transgenic animals or the benefits from their use. Nor do any of the papers indicate such phenomena are

even widespread. The skilled artisan would know how to evaluate such phenomena and could use those transgenic recombinant cells that were not susceptible to these effects in the claimed screening methods without having to resort to undue experimentation.

Kappel *et al.*, *Current Opinion in Biotech.*, 3:548-552, 1192 ("Kappel"), is cited in the Action as supporting the proposition that there is unpredictability with the sites of integration of the transgene in to the target genome. The Action contends that Kappel states that "transgenic animals are regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such as DNA methylation or deletion from the genome." Kappel on page 549, col. 2, paragraph 2. However, Kappel fails to support the Action's thesis. First, the statement in Kappel relied upon by the Action actually states, "While the investigator has the ability to target transgene expression to a *large extent*, there are inherent cellular mechanisms that *may* alter the pattern of gene expression." (Emphasis added.) This statement acknowledges that this issue raised in the Action is not widely observed and that it *may* affect expression. Applicants further note that because of the nature of the claimed invention, the screening method is looking ofr modulators of Fortilin activity of expression and thus it has a comparative aspect. Alterations in the level of expression need not affect the ability to screen for such modulators and inhibitors. Consequently, even if the remote situation where the potential problem noted by Kappel (in 1992, around eight years prior to the filing date of the present application), this does not mean the claimed invention would not work or that the entire field of transgenics was unpredictable.

Moreover, Kappel concludes by saying, "Transgenic animal technology is now *well established* as a critical method for analyzing gene expression and function." Page 551, col. 1, first paragraph. Therefore, its authors acknowledge that this technology is well established and that any problems with the technology can be readily overcome. Accordingly, this paper supports

that the claimed invention is enabled to the extent it covers recombinant cells in a transgenic animal.

The Action relies upon Mullins *et al.*, *J. Clin. Invest.* 97:1557-1560, 1996 as teaching that "the use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another." Not only is this statement limited to nonmurine transgenic animals, which is a subspecies of the embodiment that the Action takes issue with, but also this article does not say the transgenics in nonmurine species cannot be made. Moreover, it says nothing about the use of Fortilin as a transgenic gene for making a nonmurine transgenic animal. In addition, even if there could be variability that was dependent on integration sites, the Action does not explain why undue experimentation would be required, particularly in an area that is well established.

Similarly, the Action relies upon another related paper but it also does not say that the use of a recombinant cell will not work with the presently claimed invention. The reference of Mullins *et al.*, *Hypertension* 22:631, 1993, is said to indicate that integration of the transgene into different species of animals has given divergent phenotypes. However, it is unclear how this indicates it would require undue experimentation to practice the invention to the extent it covers transgenic cells. As with the later Mullins paper, the authors focus on nonmurine animals and discuss their use as animal models for hypertension and cardiovascular research. Also, the Mullins paper concludes, "Since transgenic technology has been extended to include a wide range of rodents and ruminants, the benefits for cardiovascular research and hypertensive research are clear." This paper also supports that the claimed invention is enabled to the extent it

covers cells from transgenic animals because it also highlights the overall success of using transgenic animals for research purposes.

The Cameron paper, *Molecular Biotechnology* 7:253, 1997 is said to discuss some problems with expression levels in transgenic animals. However, this paper states, "[T]ransgenic laboratory models have flourished , and the initial promise of this technology has been amply demonstrated." Page 254. Overall, this paper supports that it would not require undue experimentation to practice this one embodiment of the claimed invention. Additionally, to the extent the rejection asserts that there was unpredictability regarding the proper expression of a transgene and the variability of transgene expression in different animal species, the Cameron paper provides guidance to the skilled artisan in how to overcome these issues. It provides references and a discussion of how different groups have addressed issues related to transgene expression. The Cameron paper was published in 1997 and thus was available to the skilled artisan at the time the present specification was filed. Patent law indicates, "The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available in the public." MPEP 2164.05(a) (citing *inter alia*, *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q. 2d 1331, 1332 (Fed. Cir. 1991)).

The Action has not established that it would require undue experimentation to practice the claimed invention to the extent it covers transgenic animals. Applicants respectfully request this rejection be withdrawn.

2. Fortilin Variants

As discussed above, the claims are directed to a Fortilin polypeptide that has at least 90% identity to the amino acid sequence of SEQ ID NO:2. The scope of the claim is not very extensive and there can be at most 17 changes with respect to SEQ ID NO:2. It would not require undue experimentation to evaluate different variations in the context of the claimed method,

particularly in light of the specification which provides SEQ ID NO:2 and provides data and experimental protocols for testing the function of Fortilin.

The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.'" PPG Indus., Inc. v. Guardian Indus., Corp., 75 F.3d 1558, 1564 (Fed. Cir. 1996) (quoting Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1576 (Fed. Cir. 1984)). In this case, the amount of experimentation is not unduly extensive because of the scope of the claims, the teaching of the specification, and the knowledge of the skilled artisan at the time this application was filed.

Applicants respectfully request this rejection be withdrawn.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so they may pass to issuance.

Should the Examiner have any questions or comments, please contact the undersigned attorney at 512-536-3081.

Respectfully submitted,

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